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## TITLE

FLUOROUS TAGGING COMPOUNDS AND METHODS OF INCREASING THE  
FLUOROUS NATURE OF COMPOUNDSField of the Invention

5           The present invention relates to fluororous tagging compounds and to methods of increasing the fluororous nature of compounds.

Background of the Invention

10           Organic chemists are typically trained that organic compounds have to be synthesized as pure substances through well-planned reactions and scrupulous separation. In fields such as drug discovery, catalyst design and new material development, however, tens of thousands of organic compounds must be synthesized and tested to discover a few  
15   active ones. In the pharmaceutical industry, for example, synthesizing such a large number of compounds in the traditional way is too slow compared to the rapid emergence of new biological targets. A major factor limiting the productivity of orthodox solution (liquid) phase organic  
20   synthesis is the tedious separation process for the purification of products. High throughput organic synthesis, therefore, preferably integrates organic reactions with rapid purification/separation procedures.

Recently, fluorous synthetic and separation techniques have attracted the interest of organic chemists. In fluorous synthetic techniques, reaction components are typically attached to fluorous groups such as perfluoroalkyl groups to facilitate the separation of products. In general, fluorous-tagged molecules partition preferentially into a fluorous phase while non-tagged ones partition into an organic phase. Although fluorous synthetic and/or separation techniques are promising, such techniques are currently limited by a lack of availability of suitable fluorous tags.

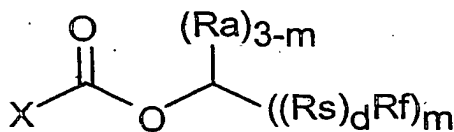
It is thus very desirable to develop fluorous tagging compounds and methods of increasing the fluorous nature of compounds.

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### Summary of the Invention

In one aspect, the present invention provides a method of increasing the fluorous nature of a compound. The method includes the step of reacting the compound with at least one second compound having the formula:

20



wherein Rf is a fluorous group (for example, a fluoroalkyl group, a fluorinated ether or another highly fluorinated

group), Rs is a spacer group, d is 1 or 0 (that is, Rs may be present or absent), m is 1, 2 or 3, Ra is an alkyl group and X is a suitable leaving group. Suitable leaving groups include, but are not limited to, a halide (F, Cl, Br or I),  
5 -N<sub>3</sub>, CN, RO-, NH<sub>2</sub>O-, NHRO-, NR<sub>2</sub>O-, RCO<sub>2</sub>-, ROCO<sub>2</sub>-, RNCO<sub>2</sub>-, RS-, RC(S)O-, RCS<sub>2</sub>-, RSC(O)S-, RSCS<sub>2</sub>-, RSCO<sub>2</sub>-, ROC(S)O-, ROCS<sub>2</sub>-, RSO<sub>2</sub>-, RSO<sub>3</sub>-, ROSO<sub>2</sub>-, ROSO<sub>3</sub>-, RPO<sub>3</sub>-, ROPO<sub>3</sub>-, an N-imidazolyl group, an N-triazolyl group, an N-benzotriazolyl group, a benzotriazolyl group, an imidazolyl group, an  
10 N-imidazolinone group, an N-imidazolone group, an N-imidazolinethione group, an N-imidazolinthione group, an N-succinimidyl group, an N-phthalimidyl group, an N-succinimidyloxy group, an N-phthalimidyloxy group, -ON=C(CN)R, or a 2-pyridyloxy group. R is preferably an  
15 alkyl group or an aryl group.

The terms "alkyl", "aryl" and other groups refer generally to both unsubstituted and substituted groups unless specified to the contrary. Unless otherwise specified, alkyl groups are hydrocarbon groups and are  
20 preferably C<sub>1</sub>-C<sub>15</sub> (that is, having 1 to 15 carbon atoms) alkyl groups, and more preferably C<sub>1</sub>-C<sub>10</sub> alkyl groups, and can be branched or unbranched, acyclic or cyclic. The above definition of an alkyl group and other definitions apply also when the group is a substituent on another  
25 group. The term "aryl" refers to phenyl (Ph) or naphthyl, substituted or unsubstituted. The terms "alkylene" refers to bivalent forms of alkyl.

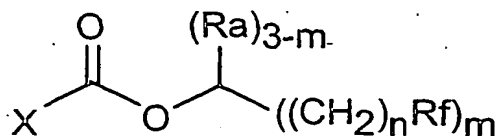
The groups set forth above, can be substituted with a wide variety of substituents. For example, alkyl

groups may preferably be substituted with a group or groups including, but not limited to, halide(s). Preferably, halide constituents are F and/or Cl. Aryl groups may preferably be substituted with a group or groups including, but not limited to, halide(s), alkyl group(s), a cyano group(s) and nitro group(s). As used herein, the terms "halide" or "halo" refer to fluoro, chloro, bromo and iodo. Preferred halide substituents are F and Cl.

The resulting fluorous "tagged" compound can be used in a variety of fluorous reaction and/or separation techniques. Such fluorous reaction and separation techniques are disclosed, for example, in U.S. Patent Nos. 5,859,247 and 5,777,121 and U.S. Patent Application Serial No. 09/506,779, assigned to the assignee of the present invention, the disclosures of which are incorporated herein by reference.

Preferably, the molecular weight of the fluorous tag of the present invention does not exceed about 2,500. More preferably, the molecular weight does not exceed about 2,000. Even more preferably the molecular weight does not exceed about 1,750. Compounds may bear more than one fluorous tag of the present invention.

In another aspect, the present invention provides a compound (a fluorous tagging compound) having the formula:



wherein Rf is a fluororous group (for example, a fluoroalkyl group, a fluorinated ether or another highly fluorinated group), n is an integer between 0 and 6, m is 1, 2 or 3, Ra is an alkyl group and X is a leaving group. Ra is preferably C<sub>1</sub>-C<sub>6</sub> alkyl group.

As used herein, the term "fluororous", when used in connection with an organic (carbon-containing) molecule, moiety or group, refers generally to an organic molecule, moiety or group having a domain or a portion thereof rich in carbon-fluorine bonds (for example, fluorocarbons or perfluorocarbons, fluorohydrocarbons, fluorinated ethers and fluorinated amines). The term "fluororous compound," thus refers generally to a compound comprising a portion rich in carbon-fluorine bonds. As used herein, the term "perfluorocarbons" refers generally to organic compounds in which all hydrogen atoms bonded to carbon atoms have been replaced by fluorine atoms. The terms "fluorohydrocarbons" and "hydrofluorocarbons" include organic compounds in which at least one hydrogen atom bonded to a carbon atom has been replaced by a fluorine atom. A few examples of suitable fluororous groups Rf for use in the present invention include, but are not limited to, -C<sub>4</sub>F<sub>9</sub>, -C<sub>6</sub>F<sub>13</sub>, -C<sub>8</sub>F<sub>17</sub>, -C<sub>10</sub>F<sub>21</sub>, -C(CF<sub>3</sub>)<sub>2</sub>C<sub>3</sub>F<sub>7</sub>, -C<sub>4</sub>F<sub>8</sub>CF(CF<sub>3</sub>)<sub>2</sub>, and -CF<sub>2</sub>CF<sub>2</sub>OCF<sub>2</sub>CF<sub>2</sub>OCF<sub>3</sub>.

As used herein, the term "tagging" refers generally to attaching a fluororous moiety or group (referred

to as a "fluorous tagging moiety" or "tagging group") to a compound to create a "fluorous tagged compound". Separation of the tagged compounds of the present invention is achieved by using fluorous separation techniques that are based upon differences between/among the fluorous nature of a mixture of compounds. As used herein, the term "fluorous separation technique" refers generally to a method that is used to separate mixtures containing fluorous molecules or organic molecules bearing fluorous domains or tags from each other and/or from non-fluorous compounds based predominantly on differences in the fluorous nature of molecules (for example, size and/or structure of a fluorous molecule or domain or the absence thereof). Fluorous separation techniques include but are not limited chromatography over solid fluorous phases such as fluorocarbon bonded phases or fluorinated polymers. See, for example, Danielson, N.D. et al., "Fluoropolymers and Fluorocarbon Bonded Phases as Column Packings for Liquid Chromatography," J. Chromat., 544, 187-199 (1991). Examples of suitable fluorocarbon bonded phases include commercial Fluofix® and Fluophase™ columns available from Keystone Scientific, Inc. (Bellefonte, PA), and FluoroSep™-RP-Octyl from ES Industries (Berlin, NJ). Other fluorous separation techniques include liquid-liquid based separation methods such as liquid-liquid extraction or countercurrent distribution with a fluorous solvent and an organic solvent.

Brief Description of the Drawings

Figure 1 illustrates synthesis and introduction of fluorous BOC groups.

5 Figure 2 illustrates synthesis of a fluorous BOC reagent of the present invention and its attachment to an amine and detachment from the resulting amide.

Figure 3 illustrates recovery of a fluorous BOC compound of the present invention.

10 Figure 4 illustrates the utility of fluorous BOC compounds of the present invention in separating a library of compounds.

Figure 5 illustrates the structure of several amides generated from fluorous BOC tagging compounds of the present invention.

15 Figure 6 illustrates several products generated by deprotection of fluorous BOC protected amines.

Figure 7 illustrates fluorous BOC groups with different fluorine content and spacer groups.

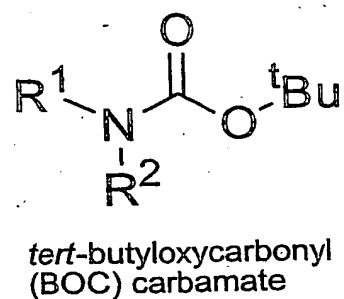
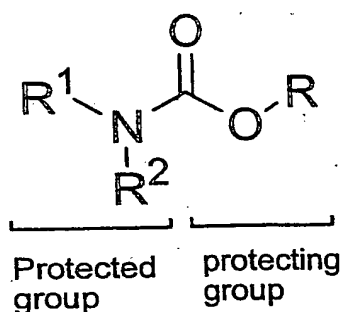
20 Figure 8 illustrates the synthesis of the 96-compound library that is described in Example 15.

Figure 9 illustrates the isolated yields of the 96-compound library of Figure 8.

### Detailed Description of the Invention

Carbamates are an important class of protecting group for nitrogen. For example, virtually all peptide synthesis schemes rely on carbamate protecting groups of some sort, and carbamates are commonly used in alkaloid synthesis and other areas. One of the most useful carbamates is the *tert*-butyloxycarbonyl group (commonly referred to as the "BOC" group) illustrated below:

A carbamate



In the present invention, a new class of fluororous carbamates referred to herein as fluororous BOC compounds or groups were synthesized after the BOC group. The fluororous tagging groups of the present invention can, for example, be reacted with nitrogen-bearing groups such as amine groups ( $-\text{NR}^1\text{R}^2$ ) of compounds to create a fluororous-tagged (or protected) compound.

The fluorous BOC (<sup>F</sup>BOC) groups of the present invention generally act like traditional BOC and other carbamate groups to protect nitrogen-based functional groups during organic reactions. Protecting groups are discussed generally in Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis; 3rd ed.; Wiley-Interscience: New York, (1999) and Kocienski, P. "Protecting groups", Thieme: Stuttgart (1994). However, the fluorous BOC groups of the present invention have advantages over other traditional carbamate and other protecting groups in that they facilitate separation of the <sup>F</sup>BOC-protected (fluorous-tagged) products from each other and from non-tagged reaction components. Additionally, the fluorous domain of the fluorous BOC groups are useful not only for attachment to nitrogen, but also to oxygen, sulfur and other heteroatoms. The resulting <sup>F</sup>BOC carbonates, thiocarbamates, etc. serve substantially the same purpose and are used analogously to the <sup>F</sup>BOC carbamates described in greater detail herein.

The reagents used for the protection of amines with fluorous BOC groups are generally prepared as shown in Figure 1. Fluorous alcohols **1a-c** bearing one, two or three fluorous chains are readily synthesized, for example, by nucleophilic addition reactions. Addition of an organometallic reagent  $R_f(CH_2)_nM$  (wherein, M is, for example, lithium, magnesium halide, etc. and  $R_f$  is a fluorous group) to an appropriate ketone generates an alcohol **1a** with one fluorous chain and two alkyl groups. Similarly, alcohols with two fluorous chains **1b** can be generated by organometallic addition to esters, acids

chlorides or related molecules, and alcohols with three fluororous chains 1c can be generated by nucleophilic additions to carbonate esters, phosgene, or related molecules. The alcohols with two and three fluororous chains prepared by these routes usually contain the same fluororous group, but alcohols with different fluororous groups can be prepared by several routes. For example, addition of  $Rf^1(CH_2)_{n1}M$  to an aldehyde followed by oxidation of the resulting secondary alcohol and addition of  $Rf^2(CH_2)_{n2}M$  results in an alcohol with two different fluororous chains ( $Rf^1$  and  $Rf^2$ ) spaced by alkylene spacers that can be the same or different. A series of fluororous alcohols with different numbers of fluorines is useful, for example, in fluororous mixture synthesis techniques. See, U.S. Patent Application Serial No.09/506,779.

Fluororous BOC reagents 3 can be prepared by one of many schemes known to those skilled in the art for the conversion of standard alcohols to activated carbamoylating agents. For example, alcohols bearing one fluororous chain and two alkyl groups can react with one of many reagents 2, which can be considered as doubly activated derivatives of carbonic acids. In Figure 1, the leaving group (X) is a part of the molecule that is cleaved in the substitution reaction. Many different leaving groups suitable for use in the present invention are known to those skilled in the art. For the purposes of this invention, leaving groups whose conjugate acids have a pKa of less than about 18 are preferred. Leaving groups whose conjugate acids have a pKa of less than about 10 are more preferred. Even more preferred are leaving groups whose conjugate acids have a

pKa of less than about 5. In a preferred method, the fluorous alcohol 1a is first reacted with the reagent 2 to displace the first leaving group to give 3. The intermediate BOC reagent 3 may be isolated prior to  
5 reaction with an amine under standard conditions, or it may be reacted directly with the amine in situ without isolation. Either or both of the acylation reactions may be catalyzed by standard catalysts known to those skilled in the art. An example on one such acylation catalyst is  
10 4-dimethylaminopyridine (DMAP). Fluorous BOC reagents with two or three fluorous chains are prepared and reacted analogously to those with one chain.

#### Reactions and Compounds in the Examples:

The synthesis of a representative fluorous BOC  
15 (<sup>F</sup>BOC) reagent 7 of the present invention and its attachment to a typical amine 8 and detachment from the resulting amide 9 are shown in Figure 2. Reaction of perfluorooctylethyl iodide with t-BuLi followed by addition of acetone and workup and chromatographic purification  
20 provided the alcohol 5 in 60% yield. Activated reagent 6 was generated according to the literature methods set forth in M. Itoh, et. al, *Bull. Chem. Soc. Jpn.*, 50, 718 (1977), and then reacted with alcohol 5. Workup and chromatography provided the representative <sup>F</sup>BOC reagent 7 as  
25 a solid. Protection of amino amide 8 with the <sup>F</sup>BOC reagent 7 was accomplished under standard conditions and gave <sup>F</sup>BOC derivative 9 in quantitative yield. <sup>F</sup>BOC-protected 9 could be deprotected to regenerate 8 by treatment with neat TFA for 40 min followed by evaporation and vacuum drying to

remove the fluorous BOC remnants and other volatile compounds. The fluorous BOC remnants can also be removed by solid phase extraction over fluorous reverse phase silica gel.

- 5           The ability to recover the fluorous BOC component for reuse is demonstrated by the results of Figure 3. Coupling of 7 with dimethyl amine provided 10 in 95% yield. Cleavage of 10 with 30/70 CH<sub>2</sub>Cl<sub>2</sub>/TFA followed by evaporation provided the trifluoroacetate 11 in 100% yield.
- 10   Trifluoroacetate 11 was hydrolyzed by treatment with lithium hydroxide in methanol to provide the starting alcohol 5 in 87% yield.

- To demonstrate the utility of the fluorous BOC group in facilitating reaction separation, a 16 compound library of amides was made by parallel synthesis as shown in Figure 4. Amines 12a-d were reacted with the <sup>F</sup>BOC reagent 7 as in Figure 2 to give <sup>F</sup>BOC protected acids 13a-d. Each of the four acids was coupled with amines 14a'-d' under standard amide formation conditions using
- 20   1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDI), N-hydroxybenzotriazole (HOBt), and triethylamine (Et<sub>3</sub>N). These reaction mixtures were purified by solid phase extraction using a commercially available semi-preparative Fluofix column. The fluorous tagged products
- 25   are readily separated from all non-tagged reaction components. Yields and structures for the coupled products 15aa'-dd' are illustrated in Figure 5.

To demonstrate the removal of the fluororous BOC group, four of the products were heated in 3N HCl/MeOH at 60°C for 16 h. All the volatile products (including the residual fluororous products) were removed by exposure to high vacuum, and then the yields of the final amine hydrochlorides were determined by NMR analysis as described in the Examples. These products are shown in Figure 6. A second library of eight amines involving the steps of <sup>18</sup>F BOC protection, amide formation with rapid purification by fluororous solid phase extraction, and removal of the <sup>18</sup>F BOC group with TFA, is also described in Example 15. The resulting secondary amines were used to make 96 tertiary amines.

The amides shown in Figure 7 were prepared to demonstrate that other fluororous BOC groups with different numbers of fluororous chains and different spacer elements could also be used. The syntheses of the respective <sup>18</sup>F BOC precursors and the amides themselves are described in the Examples. The retention times of amides 16a-c were then measured on an analytical Fluofix column, eluting with the gradient shown in Figure 7. The retention times of these amides are all longer than that of amide 9. This is expected because they have more fluorines. Under these conditions, most non-fluororous tagged organic compounds have retention times at or near the solvent front (approximately 2-3 minutes). Since 9 can be separated by fluororous solid phase extraction, it follows that the more strongly retained amides 16a-c will also be separable from non-tagged compounds by solid phase extraction.

Experimental Examples

Example 1: Authentic Sample of (3,4-Dihydro-1H-isoquinolin-2-yl)piperidin-4-yl-methanone (8). N-Trifluoroacetyl isonipecotic acid (2.56 g, 11.4 mmol),  
5 tetrahydroisoquinoline (1.82 g, 13.7 mmol), EDCI (2.63 g, 13.7 mmol), HOBT (1.85 g, 13.7 mmol) and triethylamine (1.38 g, 13.7 mmol) were stirred in dry dichloromethane (30 mL) at 25 °C for 6 h. The reaction was quenched with water and the aqueous phase was extracted with dichloromethane.  
10 The combined organic phase was dried over MgSO<sub>4</sub> and purified by column chromatography (40/60 EtOAc/hexanes). The solid obtained was stirred with excess K<sub>2</sub>CO<sub>3</sub> in MeOH at 25 °C overnight (16 h). After evaporation of MeOH, the residue was partitioned between dichloromethane and basic water.  
15 Evaporation of the organic phase gave pure product as a colorless solid (2.12 g, 76% for two steps). <sup>1</sup>H NMR (CDCl<sub>3</sub>) (mixture of two rotamers) δ 7.23 - 7.16 (m, 4H), 4.73 (s, 1H), 4.67 (s, 1H), 3.83 (t, J = 5.9 Hz, 1H), 3.74 (t, J = 5.8 Hz, 1H), 3.21 - 3.16 (m, 2H), 2.92 (t, J = 5.7 Hz, 1H),  
20 2.85 (t, J = 5.7 Hz, 1H), 2.76 - 2.67 (m, 3H), 2.29 (s, 1H), 1.80 - 1.73 (m, 4H); <sup>13</sup>C NMR (CD<sub>3</sub>OD-CDCl<sub>3</sub>) δ 175.5, 175.3, 135.8, 135.1, 134.0, 133.8, 129.6, 129.3, 127.9, 127.6, 127.4, 127.3, 127.0, 48.2, 45.8, 45.4, 44.2, 41.4, 40.2, 39.6, 39.5, 30.5, 29.5, 29.4, 29.1; LRMS: m/z (relative  
25 intensity), 244 (M<sup>+</sup>, 37%), 188 (100%), 132 (74%); HRMS: calcd. for C<sub>15</sub>H<sub>19</sub>N<sub>2</sub>O 244.1576, found 244.1574. MP: 75 - 76 °C.

Example 2: 1,5-Bis(perfluorohexyl)-3-methylpentan-3-ol. A portion of 2-perfluorohexylethyl iodide (1.0 mL) was added to a suspension of Mg powder (0.85 g, 35.0 mmol) in dry diethyl ether (5 mL) under argon. The mixture was sonicated  
5 for 30 min. To the resulting suspension, a solution of 2-perfluorohexylethyl iodide (total 7.8 mL, 31.8 mmol) in dry diethyl ether (40 mL) was added over 40 - 60 min. Upon completion of addition, the dark mixture was stirred at reflux for 1 h. After cooling down to room temperature, a  
10 solution of ethyl acetate (0.9 mL, 11.1 mmol) in diethyl ether (4.0 mL) was added slowly. The mixture was stirred at room temperature overnight before quenching with saturated aqueous  $\text{NH}_4\text{Cl}$ . The aqueous phase was extracted with diethyl ether ( $3 \times 20$  mL). The ether phase was combined and dried  
15 over  $\text{MgSO}_4$ . After evaporation of solvent, the residue was purified by column chromatography with 5:95 ethyl acetate-hexane. The title compound obtained was further recrystallized twice from chloroform to give colorless needles (5.18 g, 79%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.34 - 2.10 (m, 4H),  
20 1.89 - 1.68 (m, 4H), 1.28 (s, 3H), 1.17 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  70.5, 32.0, 26.2, 25.7 (t); IR (Nujol) 3467, 2923, 1461, 1369, 1244, 1140, 1051, 701, 521  $\text{cm}^{-1}$ ; LRMS  $m/z$ : 1491 (50%), 1145 (5%), 723 (42%), 375 (100%); HRMS found: C, 29.04%, H, 1.62%. Calcd.: C, 29.28%, 1.64%. MP: 57 - 58  $^\circ\text{C}$ .

25 Example 3: O-Bis(perfluorohexylethyl)ethyloxycarbonyloxyiminophenylacetonitrile. To a sample tube sealed under argon was charged with a solution of phosgene in toluene (0.27 mL, 0.55 mmol) and the solution was cooled to 0  $^\circ\text{C}$ . A solution of 2-hydroxyimino-2-phenylacetonitrile (75 mg, 0.51 mmol) and  
30

dimethylaniline (70 uL, 0.55 mmol) in THF (0.2 mL) and benzene (0.2 mL) was added dropwise to the ice-cooled solution. The mixture was stirred at 0 °C for 6 h. The mixture was placed in a freezer (-20 °C) overnight before  
5 returning to the ice bath. A solution of the alcohol from Example 2 (0.39 g, 0.55 mmol) and pyridine (45 uL, 0.55 mmol) in THF (3.0 mL) was added dropwise. The orange mixture was stirred at 0 °C for 6 h and allowed to warm to room temperature over night. The suspension was quenched  
10 with water and extracted with diethyl ether. The organic phase was dried over MgSO<sub>4</sub>. After removal of solvent, the residue was purified by column chromatography with 5:95 ethyl acetate-hexanes to give pure product as a white gum (223 mg, 49%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.95 (d, J = 7.5 Hz, 2H),  
15 7.61 (t, J = 7.3 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 2.42 - 2.08 (m, 8H), 1.66 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 149.7, 138.7, 133.3, 129.4, 127.6, 108.2, 86.1, 28.8, 25.6 (t), 22.8; IR (thin film): 1795, 1450, 1240, 1023, 940, 729 cm<sup>-1</sup>; FABMS m/z: 910 (M<sup>+</sup>, absent), 867 (M<sup>+</sup> - CO<sub>2</sub>, 21%), 721 (100%), 681  
20 (16%).

**Example 4: 1,7-Bis(perfluorobutyl)-4-methylheptan-4-ol.** To a solution of 3-perfluorobutylpropyl iodide (688 mg, 1.77 mmol) in a mixture of dry diethyl ether and dry hexane (25 mL, 1:1 v/v) was added <sup>t</sup>BuLi (2.2 mL, 1.7 M in pentane, 3.74  
25 mmol) at -78 °C. The mixture was stirred for 1 h during which time the temperature increased to -35 °C. After cooling to -78 °C, acetyl chloride (57 uL, 0.80 mmol) was added dropwise. The cooling bath was removed and the reaction mixture was stirred for 1 h. Water was added to

quench the reaction. After extraction with ether, the organic phase was dried over  $\text{MgSO}_4$  and evaporated to dryness. The crude product was purified by column chromatography with 5:95 ethyl acetate-hexane to give the  
5 alcohol as a yellow oil (103 mg, 23%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.19 - 2.01 (m, 4H), 1.76 - 1.68 (m, 4H), 1.67 - 1.53 (m, 4H), 1.24 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  121.8 - 110.8 (m), 72.4, 41.4, 31.3, 26.7, 15.1; LRMS m/z (relative intensity) 551 ( $\text{M}^+ - \text{Me}$ , 15%), 305 (100%); HRMS found: 551.0676, calcd. for  
10  $\text{C}_{15}\text{H}_{13}\text{F}_{18}\text{O}$ : 551.0679; IR (thin film): 3147, 2975, 1468, 1356, 1206, 880, 720  $\text{cm}^{-1}$ .

**Example 5:** 1,7-Bis(perfluorohexyl)-4-methylheptan-4-ol. This compound was prepared by the same procedure as Example 4 but ethyl acetate was used instead of acetyl chloride.  
15 Yield: 68% (white solid).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.13 - 2.04 (m, 4H), 1.76 - 1.66 (m, 4H), 1.64 - 1.53 (m, 4H), 1.24 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  122.0 - 107.0 (m), 72.4, 41.4, 31.4 (t), 26.5, 15.1;  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -81.2 (3F), -114.8 (2F), -122.4 (2F), -123.4 (2F), -124.1 (2F), -126.6 (2F); LRMS:  
20 m/z (relative intensity) 751 ( $\text{M}^+ - \text{Me}$ , 77%), 709 (24%), 405 (100%); HRMS found: 751.0570, calcd. for  $\text{C}_{19}\text{H}_{13}\text{OF}_{26}$ : 751.0566; MP: 46 - 47  $^{\circ}\text{C}$ .

**Example 6:** 4-Perfluorooctyl-2-methylbutan-2-ol (5). This compound was prepared by the same procedure as Example 4  
25 but acetone was used instead of acetyl chloride. Yield: 60% (white solid).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.32 - 2.14 (m, 2H), 1.78 - 1.73 (m, 2H), 1.29 (s, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  122.4 - 107.4 (m), 69.9, 33.5, 29.4, 26.2 (t); LRMS m/z (relative

intensity) 505 ( $M^+ - H$ , 12%), 491 ( $M^+ - Me$ , 100%); HRMS found: 491.0306; calcd. for  $C_{12}H_8F_{17}O$ : 491.0304. MP: 50 - 51 °C.

## Example

7:

O-

- 5 Bis(perfluorobutylpropyl)ethoxycarbonyloxyiminophenylacetone trile. This compound was prepared by the same procedure as Example 3. Yield: 27% (gum).  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.95 (d,  $J$  = 8.1 Hz, 2H), 7.60 (t,  $J$  = 7.2 Hz, 1H), 7.51 (t,  $J$  = 7.5 Hz, 2H), 2.20 - 1.91 (m, 8H), 1.79 - 1.71 (m, 4H), 1.62 (s, 3H);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  150.0, 138.3, 133.2, 129.4, 127.6, 121.5 - 114.8 (m), 108.4, 88.7, 37.5, 30.8 (t), 23.1, 14.8; LRMS  $m/z$  (relative intensity) 761 ( $M^+ + Na$ ), 548 (45%), 305 (100%), 287 (90%). IR (thin film): 2982, 1795, 1234, 1132, 1022, 878  $cm^{-1}$ .
- 10

## 15 Example

8a:

O-

- (Perfluorooctylethyl)isopropanoxycarbonyloxyiminophenylacetone trile (7). This compound was prepared by the same procedure as Example 3. Yield: 61% (orange solid).  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.95 (d,  $J$  = 8.1 Hz, 2H), 7.60 (t,  $J$  = 6.9 Hz, 1H), 7.51 (t,  $J$  = 7.8 Hz, 2H), 2.29 - 2.15 (m, 4H), 1.66 (s, 6H);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  150.0, 138.3, 133.3, 129.5, 127.9, 127.7, 111.0, 85.9, 31.5, 25.7;  $^{19}F$  NMR ( $CDCl_3$ )  $\delta$  -79.6 (3F), -113.2 (2F), -120.7 (6F), -121.5 (2F), -121.9 (2F), -124.9 (2F); LRMS: 634 (16%), 615 (10%), 489 (100%); MP: 76 - 78 °C.
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- 25

Example 8b. 4-(3,4-Dihydro-1H-isoquinoline-2-carbonyl)-piperidine-1-carboxylic acid

4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro-1,1,-dimethyl-undecyl ester.

A solution of compound 7 (89 mg, 0.13 mmol) and compound 8 (29 mg, 0.12 mmol) in dichloromethane (4 ml) was stirred at room temperature for 2 h. The mixture was evaporated to dryness. The residue was purified by column chromatography (3:1 EtOAc/hexanes) to give compound 9 (93 mg, 100%) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.22 - 7.14 (m, 4H), 4.74 (s, 1H), 4.68 (s, 1H), 4.23 - 4.07 (br, 2H), 3.8 (br, 1H), 3.74 (t,  $J$  = 2.9 Hz, 1H), 2.96 - 2.74 (m, 5H), 2.22 - 2.01 (m, 4H), 1.74 (br, 4H), 1.51 (s, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  173.4, 173.2, 154.2, 135.3, 133.9, 133.6, 132.6, 129.3, 128.5, 127.3, 126.9, 126.8, 126.6, 126.1, 47.5, 44.7, 43.8, 43.3, 40.2, 39.1, 38.9, 32.1, 30.0, 28.5, 26.2; LRMS: 776 ( $\text{M}^+$ , 15%), 757 (27%), 739 (22%), 243 (100%), 188 (60%), 132 (45%); HRMS: calcd. for  $\text{C}_{29}\text{H}_{29}\text{N}_2\text{O}_3\text{F}_{17}$ : 776.1907, found 776.1894. MP: 114 - 116 °C.

**Example 9:** 4-(3,4-Dihydro-1H-isoquinoline-2-carbonyl)piperidine-1-carboxylic acid 1-perfluorooctylethylisopropyl ester (16a). The fluorous Boc reagent from Example 3 (89 mg, 0.13 mmol), the compound in Example 1 (29 mg, 0.12 mmol) and triethylamine (20 mg, 20.0 mmol) were mixed in dry dichloromethane (4.0 mL) and stirred at room temperature for 2 h. After evaporation of solvent, the residue was purified by column chromatography with 30:70 ethyl acetate-hexane to give pure product as a white solid. Yield: 93 mg (96%);  $R_f$  = 0.22 (30:70 ethyl acetate-hexane);  $^1\text{H}$  NMR (mixture of two rotamers) ( $\text{CDCl}_3$ )  $\delta$  7.22 - 7.14 (m, 4H), 4.74 (s, 1H), 4.68 (s, 1H), 4.23 -

4.07 (br, 2H), 3.85 (br, 1H), 3.74 (t,  $J = 5.8$  Hz, 1H),  
2.95 - 2.74 (m, 5H), 2.22 - 2.05 (m, 4H), 1.74 (br, 4H),  
1.52 (s, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  173.4, 173.2, 154.2, 135.3,  
134.0, 133.6, 132.6, 129.3, 128.5, 127.3, 126.9, 126.8,  
5 126.6, 126.1, 122.8 - 107.3 (m), 79.9, 47.5, 44.7, 43.8,  
43.3, 40.2, 39.1, 38.9, 32.1, 30.0, 28.5, 26.2; LRMS:  $m/z$   
(relative intensity) 776 ( $\text{M}^+$ , 14%), 757 ( $\text{M}^+ - \text{F}$ , 25%), 739  
( $\text{M}^+ - 2\text{F}$ , 20%), 489 (11%), 287 (20%), 271 (24%), 243 (100%),  
188 (60%), 132 (45%); HRMS calcd. for  $\text{C}_{29}\text{H}_{29}\text{N}_2\text{O}_3\text{F}_{17}$ : 776.1907,  
10 found: 776.1894; MP: 115 °C.

**Example 10:** Compound 16b. This compound was prepared by  
the same procedure as Example 9 with the fluorous Boc  
reagent from Example 8. Yield: 79% (yellowish oil);  $^1\text{H}$  NMR  
( $\text{CDCl}_3$ )  $\delta$  7.22 - 7.14 (m, 4H), 4.74 (s, 1H), 4.68 (s, 1H),  
15 4.16 (br, 2H), 3.85 (br, 1H), 3.74 (t,  $J = 5.8$  Hz, 1H),  
2.95 - 2.74 (m, 5H), 2.18 - 2.00 (m, 6H), 1.75 - 1.60 (m,  
10 H), 1.46 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  173.4, 173.2, 154.2,  
135.3, 134.0, 133.7, 132.7, 129.5, 129.0, 128.7, 128.2,  
127.5, 127.0, 126.7, 126.3, 125.0, 123.3 - 108.7 (m), 82.7,  
20 47.6, 44.7, 43.3, 40.2, 39.0, 38.7, 38.3, 37.9, 31.4, 30.8,  
30.3, 30.0, 28.5 (t), 24.6, 23.7, 14.9 (t); LRMS:  $m/z$   
(relative intensity) 835 ( $\text{M}^+ - \text{H}$ , 35%), 817 ( $\text{M}^+ - \text{F}$ , 23%),  
548 (17%), 287 (77%), 243 (100%), 188 (72%), 132 (71%).

**Example 11:** Compound 16c. This compound was prepared by  
25 the same procedure as Example 9 with the fluorous Boc  
reagent from Example 7. Yield: 100% (white solid);  $^1\text{H}$  NMR  
( $\text{CDCl}_3$ )  $\delta$  7.22 - 7.14 (m, 4H), 4.74 (s, 1H), 4.68 (s, 1H),  
4.23 - 4.07 (br, 2H), 3.8 (br, 1H), 3.74 (t,  $J = 2.9$  Hz,

1H), 2.96 - 2.74 (m, 5H), 2.22 - 2.01 (m, 4H), 1.74 (br, 4H), 1.51 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 173.4, 173.2, 154.2, 135.3, 133.9, 133.6, 132.6, 129.3, 128.5, 127.3, 126.9, 126.8, 126.6, 126.1, 47.5, 44.7, 43.8, 43.3, 40.2, 39.1, 38.9, 32.1, 30.0, 28.5, 26.2; LRMS: 776 (M<sup>+</sup>, 15%), 757 (27%), 739 (22%), 243 (100%), 188 (60%), 132 (45%); HRMS: calcd. for C<sub>29</sub>H<sub>29</sub>N<sub>2</sub>O<sub>3</sub>F<sub>17</sub>: 776.1907, found 776.1894. MP: 114 - 116 °C.

**Example 12: Dimethyl-carbamic acid 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro-1,1-dimethylundecyl ester (10).** Dimethylamine (300 uL, 2.0 M in THF, 0.60 mmol) was added to a solution of fluorous Boc reagent 7 (101 mg, 0.15 mmol) in THF. The mixture was stirred at room temperature for 1.5 h. After evaporation of solvent, the residue was purified by column chromatography with 10:90 ethyl acetate/hexane (R<sub>f</sub> = 0.18) to give pure product (82 mg, 95%); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.87 (s, 6H), 2.24 - 1.99 (m, 4H), 1.51 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 155.5, 122.0 - 105.2 (m), 79.4, 35.9, 32.1, 26.0; LRMS: 577 (M<sup>+</sup>, 9%), 558 (M<sup>+</sup> - F, 12%), 489 (45%), 90 (70%), 72 (100%); IR (thin film): 2942, 1707, 1454, 1389, 1236, 656 cm<sup>-1</sup>.

**Example 13: Trifluoro-acetic acid 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro-1,1-dimethylundecyl ester (11).** Dimethylamine (2-perfluorooctylethyl)isopropyl carbamate 10 (251 mg, 0.44 mmol) was stirred with 1:1 CH<sub>2</sub>Cl<sub>2</sub>/TFA at room temperature overnight. After evaporation of solvent, the residue was partitioned between dichloromethane and aqueous K<sub>2</sub>CO<sub>3</sub>. The organic phase was dried over MgSO<sub>4</sub> and evaporated to give

pure product (262 mg, 100%);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.22 - 2.08 (m, 4H), 1.63 (s, 6H);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -74.6 (3F), -79.6 (2F), -113.3 (2F), -120.8 (6F), -121.6 (2F), -122.1 (2F), -125.0 (2F);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  156.4 (t), 121.5 - 105.1 (m), 86.7, 31.5, 25.7 (t), 25.0; LRMS: m/z (relative intensity) 587 ( $\text{M}^+$  - Me, 70%), 489 ( $\text{M}^+$  -  $\text{CF}_3\text{CO}_2$ , 68%), 155 (82%); HRMS calcd. for  $\text{C}_{13}\text{H}_{10}\text{F}_{17}$ : 489.0511, found: 489.0504,; IR (thin film): 2992, 1784, 1371, 1214  $\text{cm}^{-1}$ .

**Example 14: Synthesis of the Library in Figures 4 and 5.**

10 1. Piperidine-1,4-dicarboxylic acid mono-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptafluoro-1,1-dimethylundecyl) ester (13a). To a solution of fluororous Boc reagent 7 (6.2 g, 9.1 mmol) and triethylamine (1.01 g, 10.0 mmol) in THF was added a solution of  
15 isonipecotic acid (1.29 g, 10.0 mmol) in water. The mixture was stirred at room temperature overnight. After removal of solvent, the solid residue as stirred with chloroform (300 mL) and the white solid was filtered off. The organic solvent was evaporated and the residue was recrystallized  
20 from chloroform/hexane to give product (2.3 g). The mother liquid was concentrated and purified by column chromatography. The product (total: 5.24 g, 87%) was obtained as a colorless solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.97 (br, 2H), 2.99 (t,  $J$  = 10.9 Hz, 2H), 2.56 - 2.48 (m, 1H), 2.18 -  
25 1.91 (m, 6H), 1.72 - 1.59 (m, 2H), 1.51 (s, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  180.1, 154.2, 126.1 - 106.8 (m), 80.1, 43.5, 42.8, 40.8, 31.8, 27.8, 26.2, 25.8; LRMS m/z (relative intensity)

661 ( $M^+$ , 13%), 642 ( $M^+ - F$ , 41%); HRMS calcd. for  $C_{20}H_{20}NO_4F_{17}$ : 661.1148, found: 661.1146,; MP: 140 - 142 °C.

2. 3-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1,1-dimethyl-

5 undecyloxy carbonylamino) propionic acid (13b). This compound was prepared by the same procedure as Example 14.1. Yield: 51%.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  5.08 (br, 1H), 3.42 (q,  $J$  = 5.7 Hz, 2H), 2.61 (t,  $J$  = 5.6 Hz, 2H), 2.17 - 2.04 (m, 4H), 1.49 (s, 6H); LRMS  $m/z$  (relative intensity) 622 ( $M^+ +$  10 H, 6%), 584 ( $M^+ - 2F$ , 32%), 562 (74%), 489 (51%), 133 (47%), 116 (100%); HRMS: found 622.0874; calcd. for  $C_{17}H_{17}NO_4F_{17}$ : 622.0886. MP: 94 - 95 °C.

3. 4-[(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-1,1-dimethyl-undecyloxy carbonylamino)-

15 methyl] benzoic acid (13c). This compound was prepared by the same procedure as Example 14.1. Yield: 52%.  $^1H$  NMR ( $MeOH-d_4$ )  $\delta$  7.96 (d,  $J$  = 8.2 Hz, 2H), 7.36 (d,  $J$  = 8.2 Hz, 2H), 4.30 (s, 2H), 2.20 - 2.01 (m, 4H), 1.50 (s, 6H); LRMS  $m/z$  (relative intensity) 667 ( $M^+ - F$ , 59%), 547 (63%), 20 489 (54%), 196 (100%), 151 (55%). MP: 137 - 140 °C; HRMS: found: 66.0929; calcd. for  $C_{22}H_{17}NO_3F_{17}$ : 666.0937

4. (2S)-Pyrrolidine-1,2-dicarboxylic acid 1-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-

1,1-dimethylundecyl) ester (13d). This compound was 25 prepared by the same procedure as Example 14.1. Yield: 47%.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  4.37 - 4.22 (m, 1H), 3.55 - 3.35 (m, 2H), 2.26 - 1.93 (m, 8H), 1.52 - 1.47 (s, 6H);  $^{13}C$  NMR ( $MeOH-d_4$ )

$\delta$  176.6, 155.5, 120.4 - 109.2 (m), 81.6, 60.6, 47.8, 32.8, 32.0, 31.1, 27.0, 26.5, 25.3, 24.6; LRMS  $m/z$  (relative intensity) 646 ( $M^+ - H$ , 10%), 628 ( $M^+ - F$ , 16%), 489 (56%), 114 (100%), 70 (70%); HRMS calcd. for  $C_{18}H_{17}NO_2F_{17}$ : 602.0974, found: 602.0988; MP: 75 - 76 °C.

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5. General Procedure for the Synthesis of 15. To sixteen vials were added acids 13a-d (0.06 mmol), amines 14a'-d' (0.24 mmol), EDCI (0.09 mmol), HOBT (0.09 mmol) and  $Et_3N$  (0.09 mmol). Chloroform (0.5 mL) and DMF (0.5 mL) was added to each vial. These sixteen reaction mixtures were stirred at room temperature for 16 h. After concentration with a vacuum centrifuge, each reaction mixture was injected onto a preparative Fluofix™ 1EW 125 column. The column was eluted with 9:1 MeOH- $H_2O$  for 25 min and followed by pure MeOH for 20 min. The fractions of products were collected and evaporated with a vacuum centrifuge to give the sixteen compound library 15aa'-15dd', which was analyzed by  $^1H$  NMR spectroscopy. The isolated yields of the amides are listed in Figure 5.

20 15aa'  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.22 - 7.17 (m, 4H), 4.74 (s, 1H), 4.68 (s, 1H), 4.14 - 4.10 (m, 2H), 3.84 (s, 1H), 3.74 (t,  $J$  = 5.7 Hz, 1H), 2.95 - 2.74 (m, 4H), 2.24 - 2.05 (m, 4H), 1.74 (br, 4H), 1.51 (s, 6H).

25 15ab'  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.54 (d,  $J$  = 6.0 Hz, 2H), 7.16 (d,  $J$  = 5.8 Hz, 2H), 5.95 (s, 1H), 4.46 (d,  $J$  = 6.0 Hz, 2H), 4.11 (br, 2H), 2.80 (t,  $J$  = 11.8 Hz, 2H), 2.34 - 2.28 (m, 5H), 1.71 (br, 4H), 1.51 (s, 6H).

15ac  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.08 (s, 1H), 4.08 (br, 2H), 3.53 - 3.49 (m, 1H), 3.16 - 3.11 (m, 2H), 2.81 - 2.74 (m, 3H), 2.52 (br, 1H), 2.26 - 2.03 (m, 8H), 1.85 - 1.53 (m, 7H), 1.51 (s, 6H), 1.10 (t,  $J = 7.2$  Hz, 3H).

5 15ad  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.56 - 7.43 (m, 4H), 5.85 (t,  $J = 5.4$  Hz, 1H), 4.51 (d,  $J = 6.0$  Hz, 2H), 4.10 (br, 2H), 2.79 (br, 2H), 2.36 - 2.06 (m, 5H), 1.87 - 1.60 (m, 4H), 1.51 (s, 6H).

10 15ba  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.24 - 7.09 (m, 4H), 5.45 (t,  $J = 5.8$  Hz, 1H), 4.74 (s, 1H), 4.59 (s, 1H), 3.83 (t,  $J = 6.0$  Hz, 1H), 3.65 (t,  $J = 5.9$  Hz, 1H), 3.50 - 3.45 (m, 2H), 2.92 - 2.85 (m, 2H), 2.61 - 2.58 (m, 2H), 2.22 - 1.98 (m, 4H), 1.56 (s, 6H).

15 15bb  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.55 (d,  $J = 5.9$  Hz, 2H), 7.17 (d,  $J = 5.8$  Hz, 2H), 6.35 (s, 1H), 5.29 (s, 1H), 4.46 (d,  $J = 6.0$  Hz, 2H), 3.45 (q,  $J = 6.0$  Hz, 2H), 2.51 (t,  $J = 5.8$  Hz, 2H), 2.11 - 1.98 (m, 4H), 1.46 (s, 6H).

20 15bc  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.16 (br, 1H), 5.38 (s, 1H), 4.14 (br, 2H), 3.67 - 3.41 (m, 2H), 3.16 - 3.12 (m, 2H), 2.79 - 2.75 (m, 2H), 2.55 (br, 1H), 2.42 (br, 1H), 2.24 - 2.02 (m, 4H), 1.85 - 1.68 (m, 5H), 1.48 (s, 6H), 1.08 (m, 3H).

25 15bd  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.56 - 7.42 (m, 4H), 6.11 (s, 1H), 5.23 (s, 1H), 4.50 (d,  $J = 5.9$  Hz, 2H), 3.48 - 3.42 (q,  $J = 6.0$  Hz, 2H), 2.48 (t,  $J = 5.9$  Hz, 2H), 2.22 - 1.99 (m, 4H), 1.46 (s, 6H).

15ca  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 7.43 (d,  $J = 7.8$  Hz, 2H), 7.33 (d,  $J = 7.6$  Hz, 2H), 7.18 - 7.01 (m, 4H), 5.0 (br, 1H), 4.94 (br, 1H), 4.59 (br, 1H), 4.37 (m, 2H), 3.99 (br, 1H), 3.64 (br, 1H), 2.97 - 2.87 (br, 2H), 2.20 - 2.06 (m, 4H), 1.53 (s, 6H).

15cb  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.47 (s, 2H), 7.85 (d,  $J = 8.2$  Hz, 2H), 7.39 (d,  $J = 8.0$  Hz, 4H), 4.62 (s, 2H), 4.30 (s, 2H), 2.31 - 2.09 (m, 4H), 1.46 (s, 6H).

15cc  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.74 (d,  $J = 8.1$  Hz, 2H), 7.33 (d,  $J = 7.9$  Hz, 2H), 4.36 (s, 2H), 3.71 - 3.67 (m, 1H), 3.31 - 3.25 (m, 2H), 2.82 - 2.79 (m, 2H), 2.28 - 1.99 (m, 8H), 1.74 - 1.63 (m, 2H), 1.51 (s, 6H), 1.11 (t,  $J = 7.2$  Hz, 3H).

15cd  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.77 (d,  $J = 8.2$  Hz, 2H), 7.60 - 7.41 (m, 4H), 7.34 (d,  $J = 7.75$  Hz, 2H), 6.48 (s, 1H), 4.98 (s, 1H), 4.71 (d,  $J = 5.8$  Hz, 2H), 4.36 (m, 2H), 2.36 - 1.91 (m, 4H), 1.51 (s, 6H).

15da  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.26 - 7.11 (m, 4H), 4.83 - 4.58 (m, 3H), 4.10 (m, 1H), 3.70 - 3.56 (m, 3H), 2.91 - 2.84 (m, 2H), 2.24 - 1.84 (m, 8H), 1.52 (s, 6H).

15db  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.53 (d,  $J = 4.3$  Hz, 2H), 7.43 (s, 1H), 7.17 (d,  $J = 5.7$  Hz, 2H), 4.51 - 4.34 (m, 3H), 3.43 - 3.36 (m, 2H), 2.40 - 1.94 (m, 8H), 1.40 (s, 6H).

15dc  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.91 (s, 1H), 6.42 (s, 1H), 4.29 - 4.18 (m, 1H), 3.51 - 3.40 (m, 3H), 3.13 - 2.05 (m, 2H), 2.75 (m, 1H), 2.52 (m, 1H), 2.26 - 1.68 (m, 13H), 1.52 (s, 6H), 1.08 (t,  $J = 7.2$  Hz, 3H).

5 15dd  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.50 - 7.36 (m, 4H), 4.49 - 4.23 (m, 4H), 3.49 - 3.32 (m, 2H), 2.41 - 1.82 (m, 7H), 1.51 (s, 6H).

6. General Procedure for the Deprotection of 15. Amide 15 (0.05 mmol) was heated with 3N HCl/MeOH (1.0 mL) at 65 °C for 10 16 h. The mixture was evaporated and dried under high vacuum (~1 mmHg) for 16 h. The yields of products were determined by  $^1\text{H}$  NMR spectroscopy with *p*-dimethoxybenzene as an internal standard and are shown in Figure 6.

15 Amine from compound 15aa.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.21 - 7.13 (m, 4H), 4.73 (s, 1H), 4.67 (s, 1H), 3.84 (t,  $J = 5.9$  Hz, 1H), 3.75 - 3.69 (m, 1H), 3.24 (br, 2H), 2.95 - 2.78 (m, 5H), 1.79 (br, 4H).

20 Amine from compound 15bb.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.98 (d,  $J = 5.9$  Hz, 2H), 8.21 (d,  $J = 6.0$  Hz, 2H), 4.56 (s, 2H), 3.21 (m, 2H), 2.77 - 2.73 (m, 2H).

Amine from compound 15cc.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.01 (d,  $J = 8.1$  Hz, 2H), 7.60 (d,  $J = 8.1$  Hz, 2H), 4.20 (s, 2H), 3.92 - 3.58 (m, 5H), 3.30 - 3.15 (m, 2H), 2.29 - 2.02 (m, 4H), 1.41 (t,  $J = 6.9$  Hz, 3H).

Amine from compound 15dd'.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  9.00 (s, 1H), 7.83 - 7.54 (m, 4H), 4.52 (m, 2H), 4.34 - 4.29 (m, 1H), 3.73 (s, 2H), 3.43 - 3.31 (m, 1H), 2.48 - 2.42 (m, 1H), 2.11 - 1.98 (m, 2H).

- 5 Example 15. General Procedure for the Synthesis of the Library in Figures 8 and 9. Eight vials were charged with a mixture of acid 13a (330 mg, 0.50 mmol), an amine 17{1-8} (2.0 mmol), EDCI (0.70 mmol), HOBT (0.70 mmol) and triethylamine (0.70 mmol) in chloroform/DMF. The reaction
- 10 mixtures were stirred at room temperature overnight (16 h) and quenched with water. The organic phase was collected and evaporated with a vacuum centrifuge. These residues were charged onto eight short columns packed with fluororous reverse phase silica gel (5 g, bonded phase -
- 15  $\text{Si}(\text{Me})_2\text{CH}_2\text{CH}_2\text{C}_6\text{F}_{13}$ ). Each column was eluted with 80:20 MeOH- $\text{H}_2\text{O}$  (15 mL) followed by MeOH (5 mL) and diethyl ether (20 mL). The combined MeOH and ether fractions were evaporated to dryness with a vacuum centrifuge to give library 18{1-8}. A mixture of dichloromethane and TFA (1:1, 5 mL) was
- 20 added to each of these amides 18. The reaction mixtures were stirred at room temperature for 2.5 h. After removal of dichloromethane and TFA, stock solutions of the residues 19{1-8} were prepared. Each of these eight solutions in DMF was added to an array of twelve halides 20{1-12} in the
- 25 presence of diisopropylethylamine (0.5 mmol). These 96 reaction mixtures were heated at 50 °C for 48 h. After concentration, the mixtures were purified with a PrepLCMS system. In 89 out of 96 reactions, the desired products were detected by LC-MS and isolated in yields from 5 to

100% (Figure 9). Spectroscopic data for twelve members of library 21{1-8, 1-12} are listed below.

Compound 21{2,2}.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  9.3 (br, 2H), 8.04 (t,  $J = 3.3$  Hz, 1H), 7.28 (m, 2H), 7.20 (m, 2H), 6.76 (m, 2H), 6.01 (m, 2H), 3.94 (t,  $J = 4.1$  Hz, 2H), 3.47 (d,  $J = 7.1$  Hz, 2H), 3.28 (q,  $J = 4.0$  Hz, 2H), 2.97 - 2.84 (m, 4H), 2.70 (t,  $J = 4.3$  Hz, 2H), 2.32 - 2.29 (m, 1H), 2.11 - 2.05 (m, 2H), 1.84 - 1.71 (m, 4H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  172.5, 139.4, 128.6, 128.2, 126.1, 120.5, 107.9, 53.6, 51.2, 45.8, 35.0, 25.9, 25.5.

Compound 21{3,7}.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  9.21 (br, 1H), 8.50 (t,  $J = 5$  Hz, 2H), 7.32 (t,  $J = 4.5$  Hz, 2H), 7.24 (t,  $J = 4.5$  Hz, 2H), 5.82 - 5.77 (m, 1H), 5.03 (d,  $J = 10.5$  Hz, 1H), 4.98 (d,  $J = 6.1$  Hz, 1H), 4.26 (d,  $J = 3.5$  Hz, 2H), 3.51 (d,  $J = 7.1$  Hz, 2H), 3.05 - 3.01 (m, 2H), 2.89 (q,  $J = 6.6$  Hz, 2H), 2.47 - 2.44 (m, 1H), 2.05 (q,  $J = 4.3$  Hz, 2H), 1.93 (d,  $J = 8.1$  Hz, 2H), 1.84 - 1.79 (m, 2H), 1.67 - 1.60 (m, 2H), 1.37 (q,  $J = 4.5$  Hz, 2H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  172.7, 139.4, 138.0, 128.3, 127.1, 126.8, 115.3, 55.8, 51.1, 41.9, 32.5, 25.9, 25.2, 22.7.

Compound 21{2,9}.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  8.03 (s, 1H), 7.30 - 7.27 (m, 2H), 7.21 - 7.18 (m, 2H), 6.94 - 6.89 (m, 5H), 4.7 (s, 1H), 4.29 (dd,  $J = 7.0, 1.1$  Hz, 1H), 3.05 (s, 2H), 2.71 (t,  $J = 4.4$  Hz, 2H), 2.35 (s, 1H), 1.89 (m, 4H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  172.5, 139.4, 128.7, 128.3, 126.1, 121.8, 117.4, 117.2, 68.0, 65.0, 55.8, 52.4, 51.7, 35.0, 25.9.

Compound 21{4,4}  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  9.47 (s, 1H), 8.01 (t,  $J$  = 3.3 Hz, 1H), 7.37 - 7.34 (m, 2H), 7.30 - 7.25 (m, 2H), 7.10 (d,  $J$  = 5.0 Hz, 2H), 6.84 (d,  $J$  = 5.0 Hz, 2H), 3.72 (s, 3H), 3.57 (m, 2H), 3.34 - 3.31 (m, 5H), 3.00 - 2.84 (m, 4H), 2.64 (t,  $J$  = 4.4 Hz, 2H), 2.37 - 2.32 (m, 1H), 1.89 - 1.73 (m, 3H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  172.5, 157.7, 136.9, 131.2, 129.7, 128.8, 126.9, 114.1, 113.7, 56.6, 55.1, 51.2, 34.2, 29.5, 25.9.

Compound 21{1,1}.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  8.41 (t,  $J$  = 3.5 Hz, 1H), 7.15 (d,  $J$  = 5.1 Hz, 2H), 6.88 (d,  $J$  = 5.1 Hz, 2H), 4.25 - 4.19 (m, 6H), 3.72 (s, 3H), 3.01 (s, 2H), 1.92 (br, 4H), 1.24 (t,  $J$  = 4.2 Hz, 3H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  172.5, 165.9, 158.2, 131.3, 128.5, 113.7, 61.9, 55.1, 41.4, 25.6, 13.9.

Compound 21{6,10}.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  8.54 (t,  $J$  = 3.5 Hz, 1H), 7.78 - 7.72 (m, 2H), 7.69 - 7.57 (m, 4H), 7.50 - 7.44 (m, 3H), 7.37 - 7.31 (m, 3H), 4.31 - 4.25 (m, 4H), 3.41 (d,  $J$  = 7.1 Hz, 2H), 2.99 - 2.95 (m, 2H), 2.50 - 2.47 (m, 1H), 1.97 - 1.80 (m, 4H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  172.7, 139.9, 138.8, 138.6, 133.3, 132.5, 129.0, 127.8, 126.9, 126.6, 57.7, 50.9, 41.7, 25.8.

Compound 21{5,3}.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  11.0 (s, 1H), 10.2 (s, 1H), 7.62 - 7.57 (m, 3H), 7.51 (d,  $J$  = 4.5 Hz, 2H), 7.38 (d,  $J$  = 4.8 Hz, 2H), 7.25 (s, 1H), 7.12 - 7.09 (m, 1H), 7.04 - 7.01 (m, 1H), 3.72 (d,  $J$  = 7.1 Hz, 2H), 3.14 - 3.11 (m, 2H), 3.03 (q,  $J$  = 6.7 Hz, 2H), 2.66 - 2.60 (m, 1H), 2.09 - 1.86

(m, 4H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  171.9, 138.4, 136.3, 131.5, 126.6, 123.2, 121.3, 121.1, 118.5, 118.2, 114.9, 111.6, 108.9, 56.1, 51.0, 25.8, 19.8.

5 **Compound 21{8,12}**.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  8.05 (s, 1H), 7.87 (d,  $J = 4.5$  Hz, 2H), 7.63 (d,  $J = 4.5$  Hz, 2H), 7.57 (d,  $J = 4.2$  Hz, 2H), 7.47 - 7.42 (m, 3H), 7.36 - 7.33 (m, 1H), 7.27 (d,  $J = 4.7$  Hz, 2H), 4.98 (s, 4H), 3.52 - 3.49 (m, 2H), 3.02 - 3.00 (m, 2H), 2.76 (t,  $J = 4.3$  Hz, 2H), 2.39 (s, 3H), 1.90 (br, 4H).

10 **Compound 21{5,11}**.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  9.2 (s, 1H), 8.04 (d,  $J = 4.5$  Hz, 1H), 7.30 (s, 1H), 7.26 (d,  $J = 5.7$  Hz, 1H), 7.02 (d,  $J = 5.0$  Hz, 1H), 3.93 (s, 1H), 3.51 (d,  $J = 7.2$  Hz, 2H), 3.06 - 3.02 (m, 2H), 2.93 - 2.78 (m, 4H), 2.56 - 2.53 (m, 2H), 2.38 - 2.35 (m, 1H), 1.88 - 1.76 (m, 5H), 1.64  
15 - 1.50 (m, 3H), 0.90 (d,  $J = 4.6$  Hz, 6H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  172.3, 138.4, 134.1, 131.2, 130.9, 128.4, 118.6, 54.5, 51.1, 44.3, 34.3, 31.9, 27.9, 26.9, 26.0, 25.9, 25.7, 22.1.

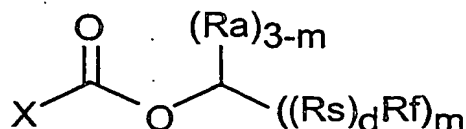
**Compound 21{5,5}**.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  8.04 (d,  $J = 4.5$  Hz, 1H), 7.35 - 7.26 (m, 4H), 7.04 - 6.99 (m, 4H), 4.33 (t,  $J = 2.8$  Hz, 2H), 3.94 - 3.92 (m, 1H), 3.61 (d,  $J = 7.2$  Hz, 2H),  
20 3.57 (s, 2H), 3.04 - 3.02 (m, 2H), 2.94 - 2.89 (m, 1H), 2.87 - 2.78 (m, 2H), 2.56 - 2.53 (m, 1H), 2.40 - 2.37 (m, 1H), 1.90 - 1.84 (m, 4H), 1.64 - 1.62 (m, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$   
25 172.3, 157.5, 138.4, 134.1, 131.2, 130.9, 129.6, 128.4, 121.4, 118.6, 114.7, 62.0, 55.0, 51.8, 44.3, 34.3, 27.9, 26.9, 25.9.

Compound 21{1,8}.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  8.42 (t,  $J$  = 3.4 Hz, 1H), 7.15 (d,  $J$  = 5.1 Hz, 2H), 6.87 (d,  $J$  = 5.2 Hz, 2H), 4.19 (d,  $J$  = 3.3 Hz, 2H), 3.72 (s, 3H), 2.94 (t,  $J$  = 6.9 Hz, 2.84 (t,  $J$  = 4.5 Hz, 1H), 2.74 (t,  $J$  = 4.5 Hz, 1H), 2.4  
5 (m, 1H), 1.93 - 1.77 (m, 4H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  171.6, 170.6, 169.5, 130.3, 127.5, 112.7, 54.1, 50.9, 50.4, 40.4, 27.7, 27.4, 25.0.

Although the present invention has been described  
in detail in connection with the above examples, it is to  
10 be understood that such detail is solely for that purpose  
and that variations can be made by those skilled in the art  
without departing from the spirit of the invention except  
as it may be limited by the following claims.

WHAT IS CLAIMED IS:

1. A method of increasing the fluorous nature of a compound, including the step of reacting the compound with at least one second compound having the formula:

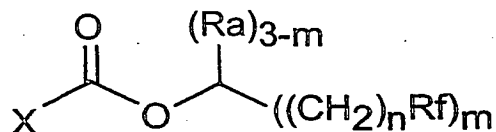


wherein Rf is a fluorous group, Rs is a spacer group, d is 1 or 0, m is 1, 2 or 3, Ra is an alkyl group and X is a leaving group.

2. The method of Claim 1 wherein the leaving group is a halide, -N<sub>3</sub>, -CN, RO-, NH<sub>2</sub>O-, NHRO-, NR<sub>2</sub>O-, RCO<sub>2</sub>-, ROCO<sub>2</sub>-, RNCO<sub>2</sub>-, RS-, RC(S)O-, RCS<sub>2</sub>-, RSC(O)S-, RSCS<sub>2</sub>-, RSCO<sub>2</sub>-, ROC(S)O-, ROCS<sub>2</sub>-, RSO<sub>2</sub>-, RSO<sub>3</sub>-, ROSO<sub>2</sub>-, ROSO<sub>3</sub>-, RPO<sub>3</sub>-, ROPO<sub>3</sub>-, an N-imidazolyl group, an N-triazolyl group, an N-benzotriazolyl group, a benzotriazolyloxy group, an imidazolyloxy group, an N-imidazolinone group, an N-imidazolone group, an N-imidazolinethione group, an N-succinimidyl group, an N-phthalimidyl group, an N-succinimidyloxy group, an N-phthalimididyloxy group, -ON=C(CN)R, or a 2-pyridyloxy group, wherein R is an alkyl group or an aryl group.

3. The method of Claim 1 wherein Rs is an alkylene group.

4. The method of Claim 4 wherein Rs is  $-\text{CH}_2\text{CH}_2-$ .
5. The method of Claim 1 wherein Ra is a  $\text{C}_1\text{-C}_6$  alkyl group.
6. The method of Claim 1 wherein the fluorous group is a perfluorocarbon, a fluorohydrocarbon, a fluorinated ether or a fluorinated amine.
7. The method of Claim 1 wherein fluorous group is a perfluoroalkyl group.
8. A compound having the formula:



wherein Rf is a fluorous group, n is an integer between 0 and 6, m is 1, 2 or 3, Ra is an alkyl group and X is a leaving group.

9. The compound of Claim 8 wherein the leaving groups is a halide,  $-\text{N}_3$ ,  $-\text{CN}$ ,  $\text{RO}-$ ,  $\text{NH}_2\text{O}-$ ,  $\text{NHRO}-$ ,  $\text{NR}_2\text{O}-$ ,  $\text{RCO}_2-$ ,  $\text{ROCO}_2-$ ,  $\text{RNCO}_2-$ ,  $\text{RS}-$ ,  $\text{RC(S)O}-$ ,  $\text{RCS}_2-$ ,  $\text{RSC(O)S}-$ ,  $\text{RSCS}_2-$ ,  $\text{RSCO}_2-$ ,  $\text{ROC(S)O}-$ ,  $\text{ROCS}_2-$ ,  $\text{RSO}_2-$ ,  $\text{RSO}_3-$ ,  $\text{ROSO}_2-$ ,  $\text{ROSO}_3-$ ,  $\text{RPO}_3-$ ,  $\text{ROPO}_3-$ , an N-imidazolyl group, an N-triazolyl group, an N-benzotriazolyl group, a benzotriazolyloxy group, an imidazolyloxy group, an N-imidazolinone group, an N-imidazolone group, an N-imidazolinethione group, an

N-succinimidyl group, an N-phthalimidyl group, an N-succinimidyloxy group, an N-phthalimidyloxy group,  $-ON=C(CN)R$ , or a 2-pyridyloxy group, wherein R is an alkyl group or an aryl group.

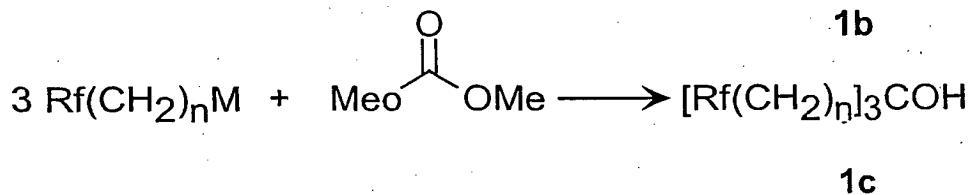
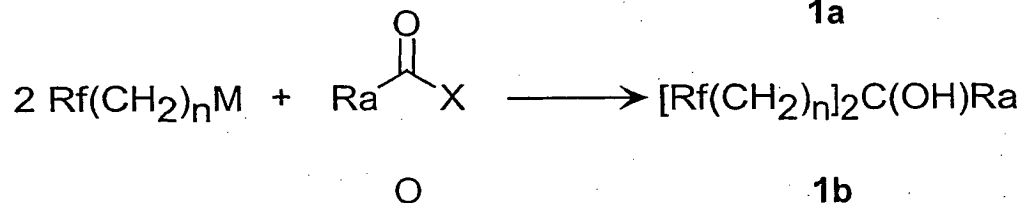
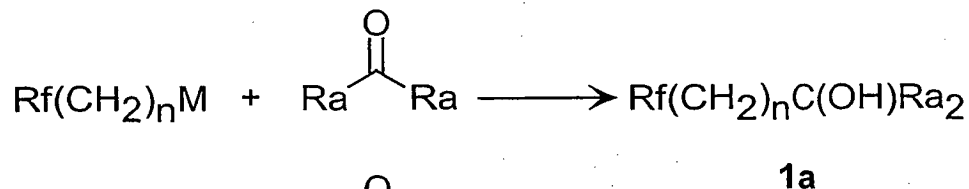
10. The compound of Claim 9 wherein  $R_a$  is a  $C_1-C_6$  alkyl group.

11. The compound of Claim 8 wherein the fluorous group is a perfluorocarbon, a fluorohydrocarbon, a fluorinated ethers or a fluorinated amine.

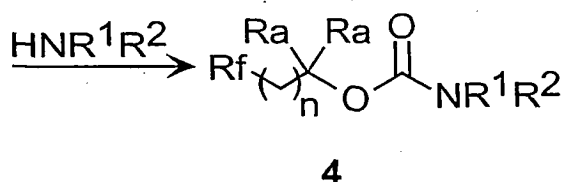
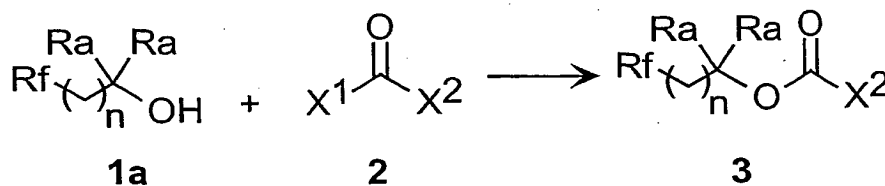
12. The compound of Claim 11 wherein fluorous group is a perfluoroalkyl group.

13. The compound of Claim 8 wherein X is Cl,  $N_3$  or  $-ON=C(CN)Ph$ .

1/9

*Preparations of alcohols*

M = Mg or Li; X = Cl or OR'; n = 2 or 3; Rf = C<sub>n</sub>F<sub>2n+1</sub>

*Preparations of Boc reagents and reaction with amines*

Fluorous Boc protected derivatives

Figure 1

2/9

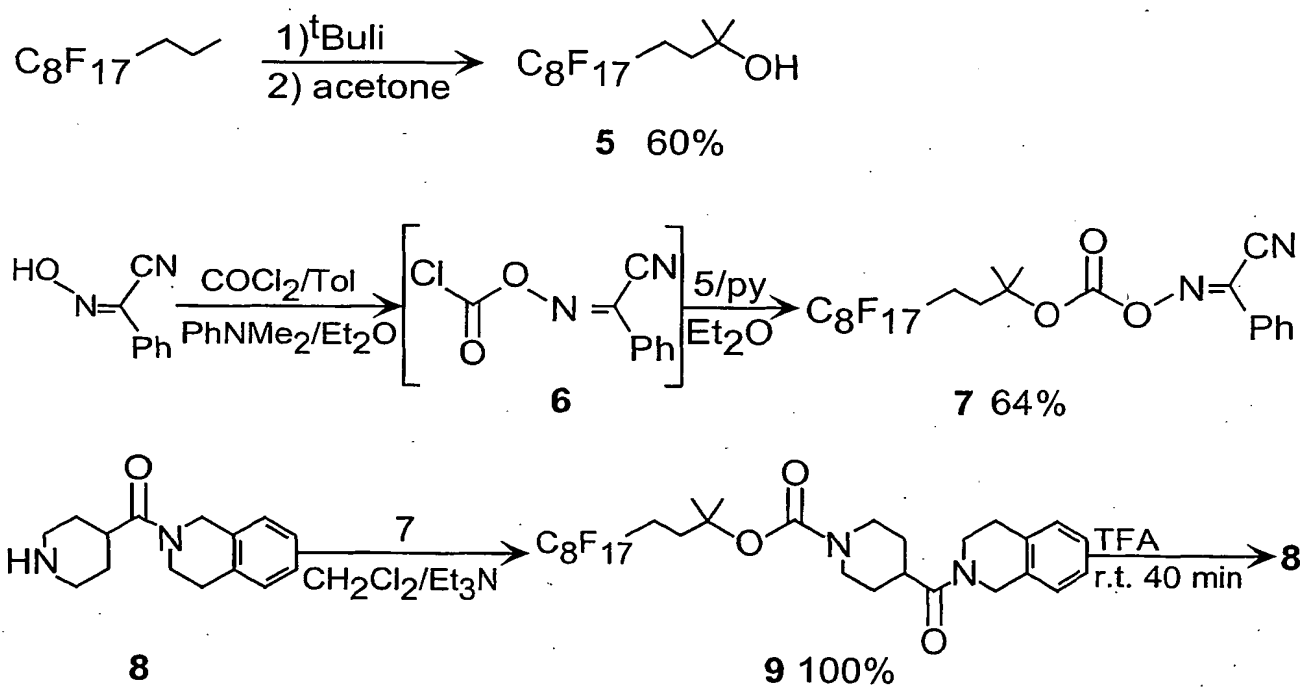


Figure 2

3/9

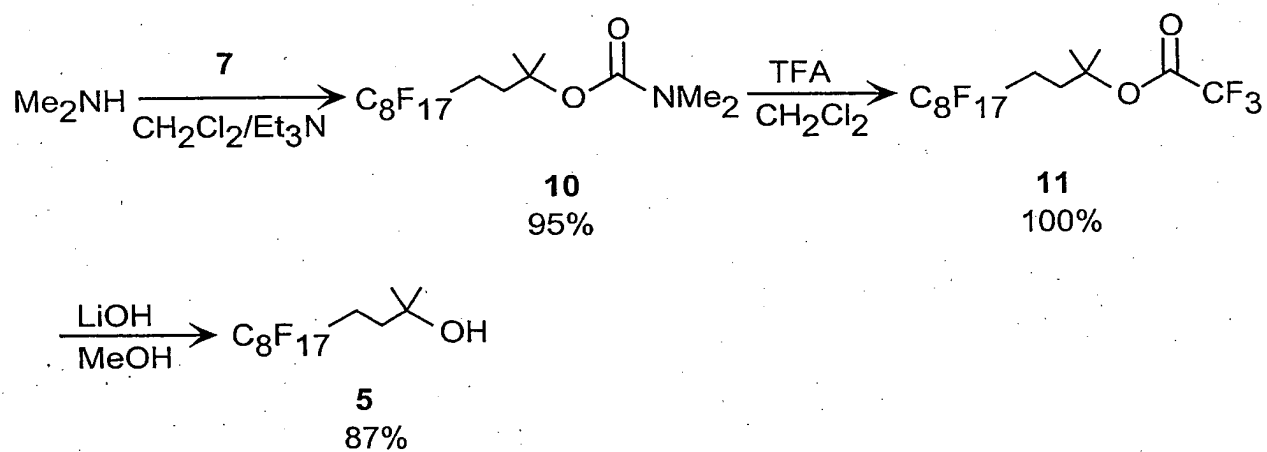
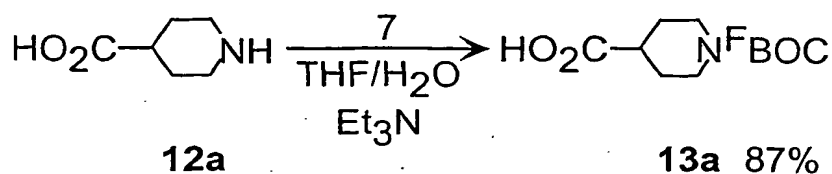
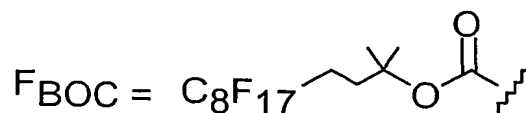
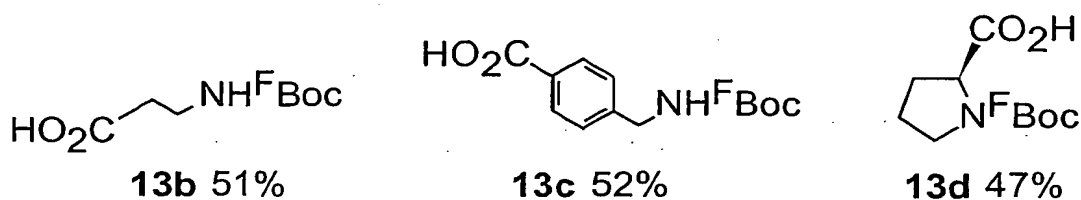


Figure 3

4/9

Examples of <sup>F</sup>Boc protectionSimilarly prepared from the corresponding amino acids **12b-c**

Examples of amide formation

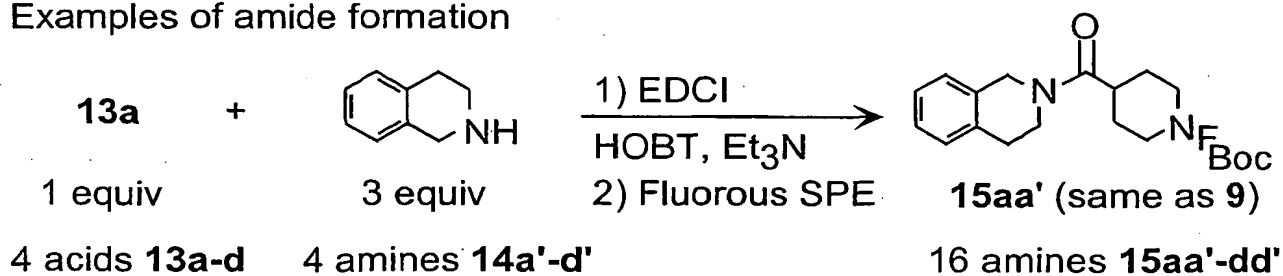
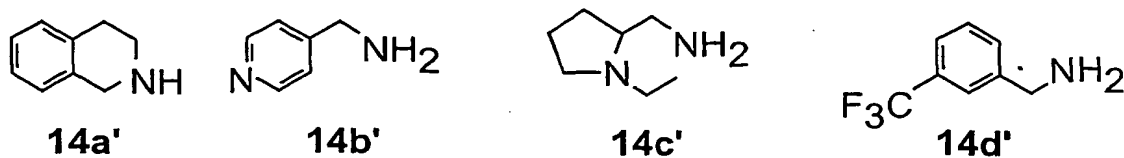
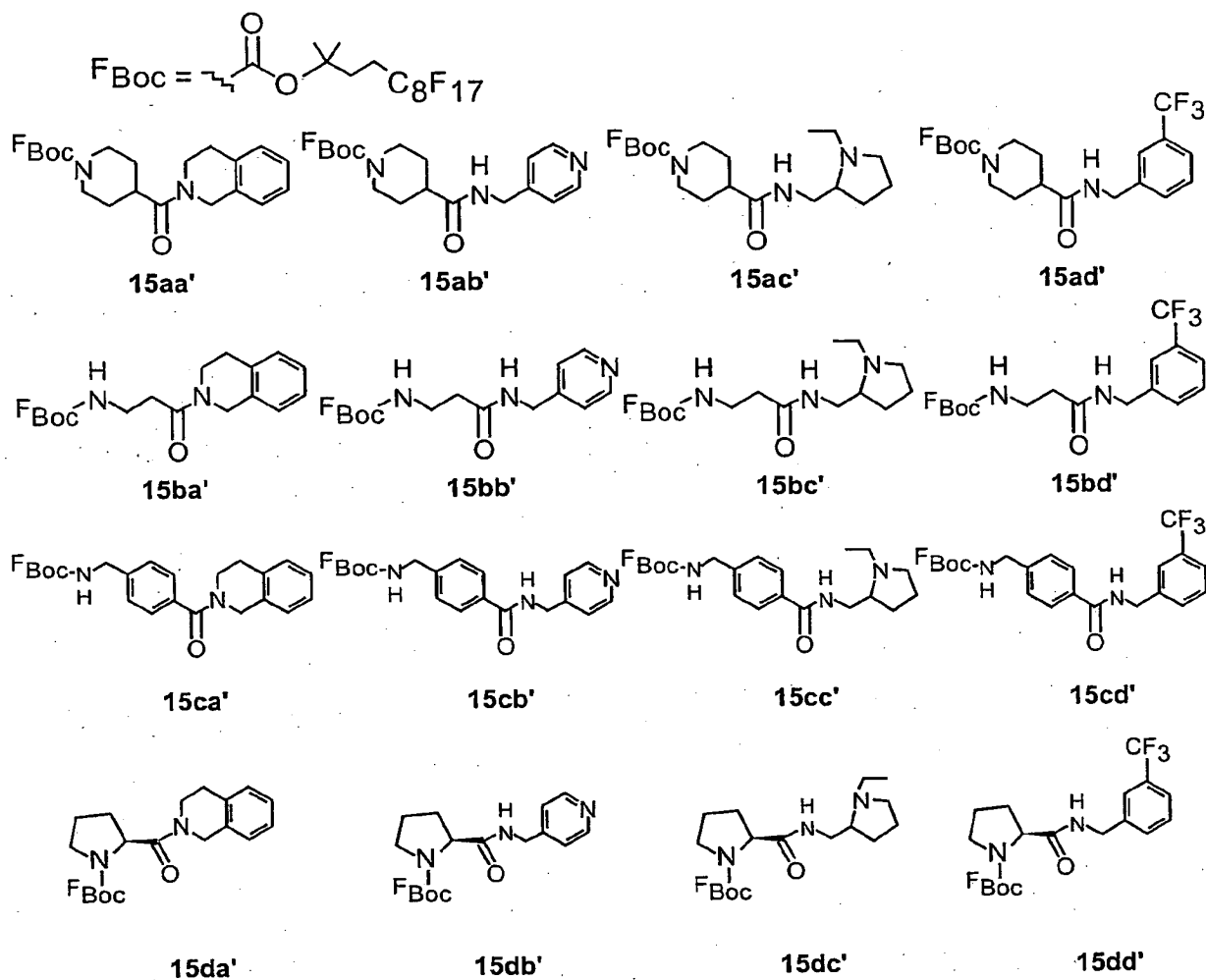
Structures of amines **14a'-d'**

Figure 4

5/9



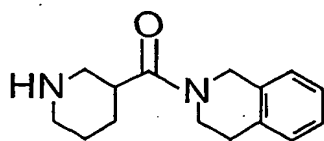
Yields of products 15

13 \ 14				
	a	b	c	d
a'	71	82	21	quan.
b'	44	98	88	81
c'	37	23	94	59
d'	31	77	73	87

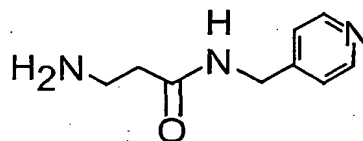
Figure 5

6/9

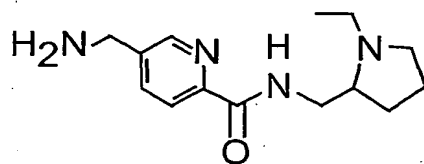
Products generated by deprotection of the fluororous Boc protected amides with HCl/MeOH



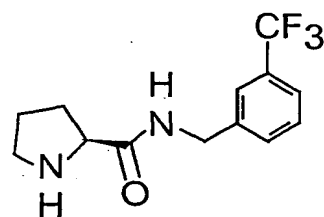
from **53aa'** 92%



from **15bb'** 100%



from **15cc'** 53%

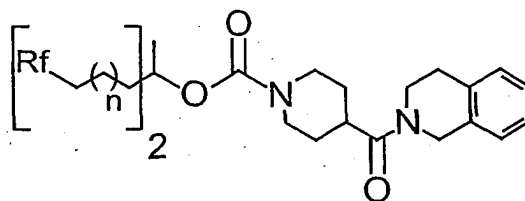


from **15dd'** 86%

Yields determined by <sup>1</sup>H NMR spectroscopy with the corresponding hydrochloride salts.

Figure 6

7/9



	Rf	n
<b>16a</b>	C <sub>6</sub> F <sub>13</sub>	0
<b>16b</b>	C <sub>6</sub> F <sub>13</sub>	1
<b>16c</b>	C <sub>4</sub> F <sub>9</sub>	1

## HPLC retention times on a Fluofix column

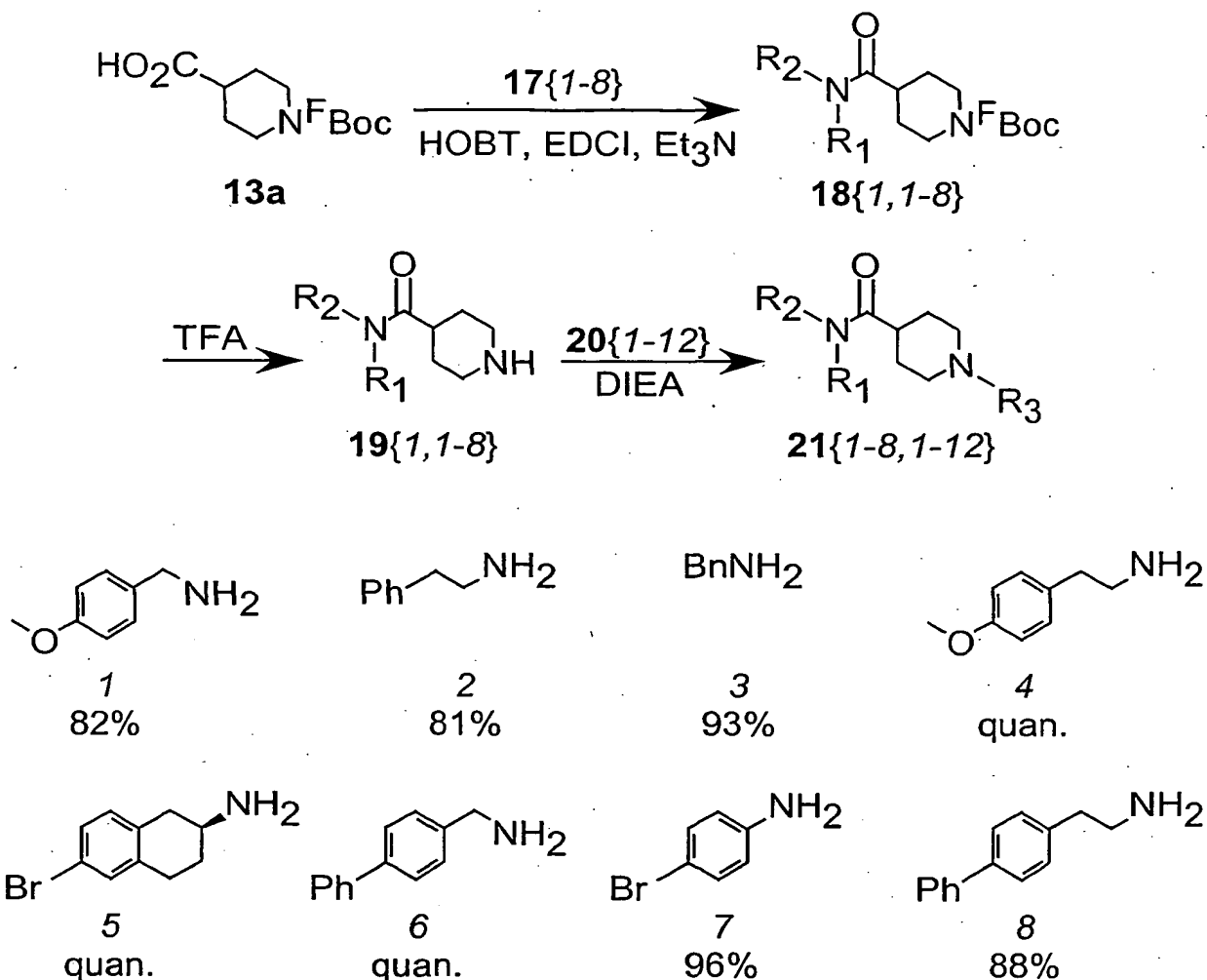
Compound retention time (min)<sup>a)</sup>

<b>9</b>	22.5
<b>16a</b>	33.8
<b>16b</b>	33.4
<b>16c</b>	24.1

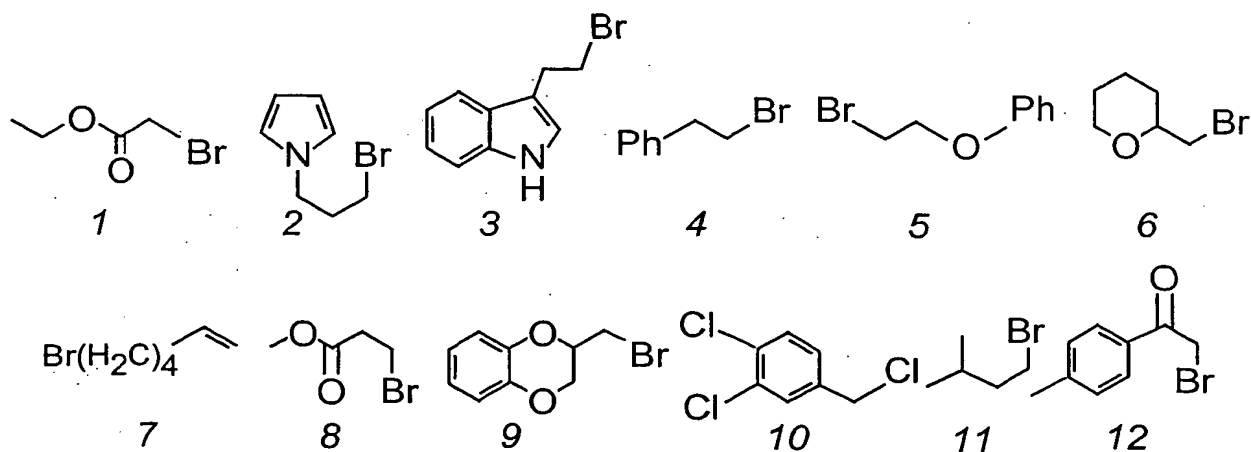
a) HPLC method: MeOH:H<sub>2</sub>O (4:1), 30 min gradient to 100% MeOH, 10 min gradient to MeOH:THF (9:1)

Figure 7

8/9



Diversity reagents 17{1-8}



Diversity reagents 20{1-12}

Figure 8

SUBSTITUTE SHEET (RULE 26)

9/9

	19{1}	19{2}	19{3}	19{4}	19{5}	19{6}	19{7}	19{8}
20{1}	(70)	quan.	94	quan.	89	95	5	60
20{2}	71	(80)	84	80	61	70	48	48
20{3}	48	58	0	65	10	41	(30)	28
20{4}	(46)	62	85	(50)	50	43	36	32
20{5}	56	72	68	52	(48)	47	41	41
20{6}	12	9	10	10	0	9	0	(9)
20{7}	51	63	(71)	54	51	60	0	36
20{8}	72	82	83	94	81	82	5	56
20{9}	13	(18)	17	10	0	14	0	11
20{10}	61	77	68	81	52	(71)	11	40
20{11}	49	63	62	49	(44)	45	5	32
20{12}	27	38	31	32	0	25	14	(14)

All compounds were characterized by LCMS. Compound with yields in parentheses were also characterized by proton NMR spectroscopy

Figure 9

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International Bureau



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LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,  
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,  
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(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
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patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,  
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

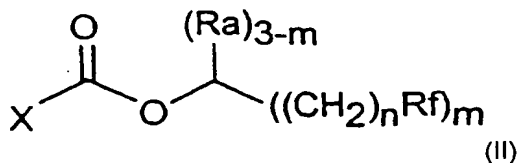
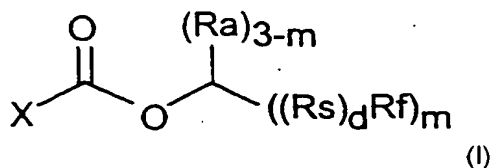
**Published:**

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2 May 2002

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: FLUOROUS TAGGING COMPOUNDS AND THEIR USE



(57) Abstract: A method of increasing the fluororous nature of a compound includes the step of reacting the compound with at least one second compound having formula (I) wherein Rf is a fluororous group, Rs is a spacer group, d is 1 or 0, m is 1, 2 or 3, Ra is an alkyl group and X is a suitable leaving group. A compound has formula (II) wherein Rf is a fluororous group, n is an integer between 0 and 6, m is 1, 2 or 3, Ra is an alkyl group and X is a leaving group.

WO 01/85675 A3

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/14350

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C269/04 C07C255/33 C07C281/00 C07C69/96 C07B61/00  
C07D401/06 C07D401/12 C07D211/60 C07D207/16

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07B C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 732 274 A (FOX W ET AL) 8 May 1973 (1973-05-08) examples 2,8 claim 1	8-13
X	GB 1 149 280 A (ICI LTD) 23 April 1969 (1969-04-23) (C2F5)3COC(O)C1 example 2	8,9, 11-13
X	US 3 627 799 A (ANDERSON LOWELL R ET AL) 14 December 1971 (1971-12-14) (CF3)3COC(O)C1 example 6	8,9, 11-13
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
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- \*O\* document referring to an oral disclosure, use, exhibition or other means
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\*X\* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

23 January 2002

Date of mailing of the international search report

19/02/2002

Name and mailing address of the ISA

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Authorized officer

Diederer, J

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/14350

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CAPLUS 'Online!  CHEMICAL ABSTRACTS SERVICE, COLUMBUS,  OHIO, US;  BASKAKOV Y.A ET AL: "Preparation of  N-(hydroxyalkyl)- and  N-(aminocarbonyloxy)alkyl)carbamates as  stress-reducing plant growth regulators. "  retrieved from  Database accession no. 1991:558738  XP002186516  Compounds with RN 136205-26-0, 136205-25-9  abstract  -&amp; WO 91 07381 A (VNII KHIM ET AL)  30 May 1991 (1991-05-30)</p>	8-13
A	<p>HUDLICKY M: "NEW SYNTHESIS AND REACTIONS  OF PERFLUORO-TERT-BUTYL CHLOROFORMATE"  JOURNAL OF FLUORINE CHEMISTRY, ELSEVIER  SEQUOIA, LAUSANNE, CH,  vol. 20, 1982, pages 649-658; XP001011888  ISSN: 0022-1139</p>	1
X	<p>abstract    Experimental, Carbamates IIIe and IIIf  from I</p>	8,9, 11-13
A	<p>CURRAN, D.P.; LUO, Z.: "Fluorous  Synthesis with FEwer Fluorines (Light  Fluorous Synthesis): Separation of Tagged  from Untagged Products by Solid-Phase  Extraction with Fluorous Reverse-Phase  Silica Gel"  J. AM. CHEM. SOC.,  vol. 121, 1999, pages 9069-72, XP002186512  abstract  Amides 1a-i (prepared via standard  acylation reaction with the corresponding  acid chloride, see supporting information  S4)  page 9070, left-hand column -right-hand  column</p>	1,8
A	<p>STUDER, A ET AL.: "Fluorous Synthesis: A  fFluorous-Phase Strategy for Improving  Separation Efficiency in Organic  Synthesis"  SCIENCE,  vol. 275, 1997, pages 823-6, XP002186513  abstract  The use of fluorinated silyl protecting  group and extraction in FC-72 (mixture  fluorinated hexanes)  figure 2</p>	1,8

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-12 (partially)

Present claims 1-12 relate to an extremely large number of possible compounds and methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds and methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds and methods in which X, as defined in claims 1 and 8, is Cl, N3 or  $\text{-ON=C(CN)Ph}$  (see claim 13).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/14350

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3732274	A	08-05-1973	NONE
GB 1149280	A	23-04-1969	NONE
US 3627799	A	14-12-1971	NONE
WO 9107381	A	30-05-1991	WO 9107381 A1 30-05-1991
		AU 625383 B2	09-07-1992
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